Synthesis and characterization of half-sandwich complexes with salicylaldimine ligand derivatives

Ujala Mahmud

Degree Project in Inorganic Chemistry, 2021
Department of Chemistry
Lund University
Sweden

BSc, 30 hp

Supervisor:
Yong Li

Examiner:
Ebbe Nordlander

Innehållsförteckning:

Abstract

New half-sandwich complexes of pentamethylcyclopentadienyl-rhodium, iridium, and *p*-cymene-ruthenium have been synthesized and characterized. All metal complexes contain ligands based on a 4-chloroquinoline framework analogous to the antimalarial drug chloroquine. The first reaction in the preparation of a new ligand is a nucleophilic substitution at the chloro position of 4-chloro-7-fluoroquinoline by a Schiff base condensation. The salicylaldimine ligand derivatives are synthesized by a Schiff base condensation from N^1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine and determined 2-hydroxy-benzaldehydes in ethanol which leads to the formation of $\mathbf{HL}_{SAL(H)}$, $\mathbf{HL}_{SAL(F)}$, $\mathbf{HL}_{SAL(Cl)}$, $\mathbf{HL}_{SAL(Br)}$, and $\mathbf{HL}_{SAL(I)}$ ligands. Furthermore, these ligands will then be used to coordinate with the metal dimers $[Ir(Cp^*)Cl_2]_2$, $[Rh(Cp^*)Cl_2]_2$, and $[Ru(p\text{-cymene})Cl_2]_2$ to synthesize the different metal complexes. Due to the startingmaterial 4-chloro-7-fluoroquinoline not reacting with various ligands along with the metal complexes, no metal complexes could be obtained. Instead, another starting material was utilized for further examination.

1 Introduction

In 2019, 229 million cases of malaria and 409.000 deaths were estimated, according to the World malaria report. Malaria has thus evolved to be one of the most deadly infectious diseases, right behind HIV/AIDS and tuberculosis. Malaria has been plaguing the humanity for 500 000 years [1]. Even though the disease is centuries old, it is still a global problem. Malaria inordinately affects the underprivileged. The majority of deaths occur amidst children, and only 20 % of all malaria-related child deaths in Africa are reported [2]. The most affected areas are Africa, South America, and East Asia, although other countries are also afflicted.

1.1 Plasmodium and life cycle:

Malaria is a disease provoked by parasites of the *Plasmodium* family and is transmitted by the bite of an infected mosquito. Only a female mosquito of the *Anopheles* can transmit the disease. The disease symptoms vary but include headache, vomiting, fever in severe cases, coma, and death. Four different types of malaria parasites are infectious in humans, *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale,* and *Plasmodium malariae.* The parasites that are the most accountable for malaria deaths are *P. falciparum* and *P. vivax*, where P. *falciparum* is responsible for the cruelest deaths in sub-Saharan Africa [1].

Plasmodium can be described as a genus of intracellular parasitic protozoa, single-celled eukaryotes with nuclei that store genetic information. A mosquito affected by the *Plasmodium* parasite does not die because mosquitoes do not have red blood cells like vertebrates in which the parasite lives and develops. The parasite transmission occurs when the female *Anopheles* mosquitoes take up the *P.* parasite from infected vertebrates, the acquired blood is vital for the nurture of their eggs. After the bite, the parasite reproduces and evolves inside the *Anopheles* mosquito. When the infected mosquito bites and sucks blood again, the parasite, embodied in their salivary glands, then proceeds to pass into the person being bitten, which is now infected. One to two weeks after being infected, the first symptoms manifest, and if not treated at once with beneficial treatment, the *P.* parasite damages the red blood cells. It clogs the capillaries, which then further leads to death [1].

The life cycle of *Plasmodium* requires two different hosts to achieve their life cycle. The distinct stages in the life cycle are very complex, where various stages can only occur in the vertebrate host and several in the mosquito vector. The process consists of both sexual and asexual cycles that appear in the vector and the host cooperatively. Before the insect transmits the parasite into the human host, the gametocyte integrates into the mosquito to form the zygote. In the course of an infected mosquito biting a human host, it transmits sporozoites from its salivary glands into the person's bloodstream. For the parasite to migrate to the salivary gland, a molecular and cellular change needs to occur where zygotes develop into ookinetes, the ookinetes are then capable of active movement. The ookinetes then allow the parasite to migrate from the mosquito midgut to the salivary gland. For the midgut to be able to develop sporozoites, the oocysts go through further division. After 8 to 15 days, the oocysts unfold to release the sporozoites, enabling them to migrate and invade the insect's salivary glands [6]. The blood then transfers the sporozoites into the liver, where they infect hepatocytes. The sporozoites then mature in the hepatocyte, and the *plasmodium* parasite forms into numerous schizonts. Eventually, each schizont is multiplied into various daughter cells called merozoites. The merozoites then withdraw from the liver and reenter the bloodstream, where they attack the red blood cells, grow and divide moreover—simultaneously destroying the blood cells. It takes about 24 hours for *P. knowlesi* to invade the red blood cell and rupture the cell, which is the shortest life cycle [7].

Merozoites reproduce both asexually and sexually. The gametocytes will only mate when the *Anopheles* mosquito bites the infected human host. When two gametocytes breed, it produces an embryonic form called ookinetes. Subsequently, it opens up, and numerous sporozoites migrate to the insect's salivary glands, ready to infect another person in the cycle.

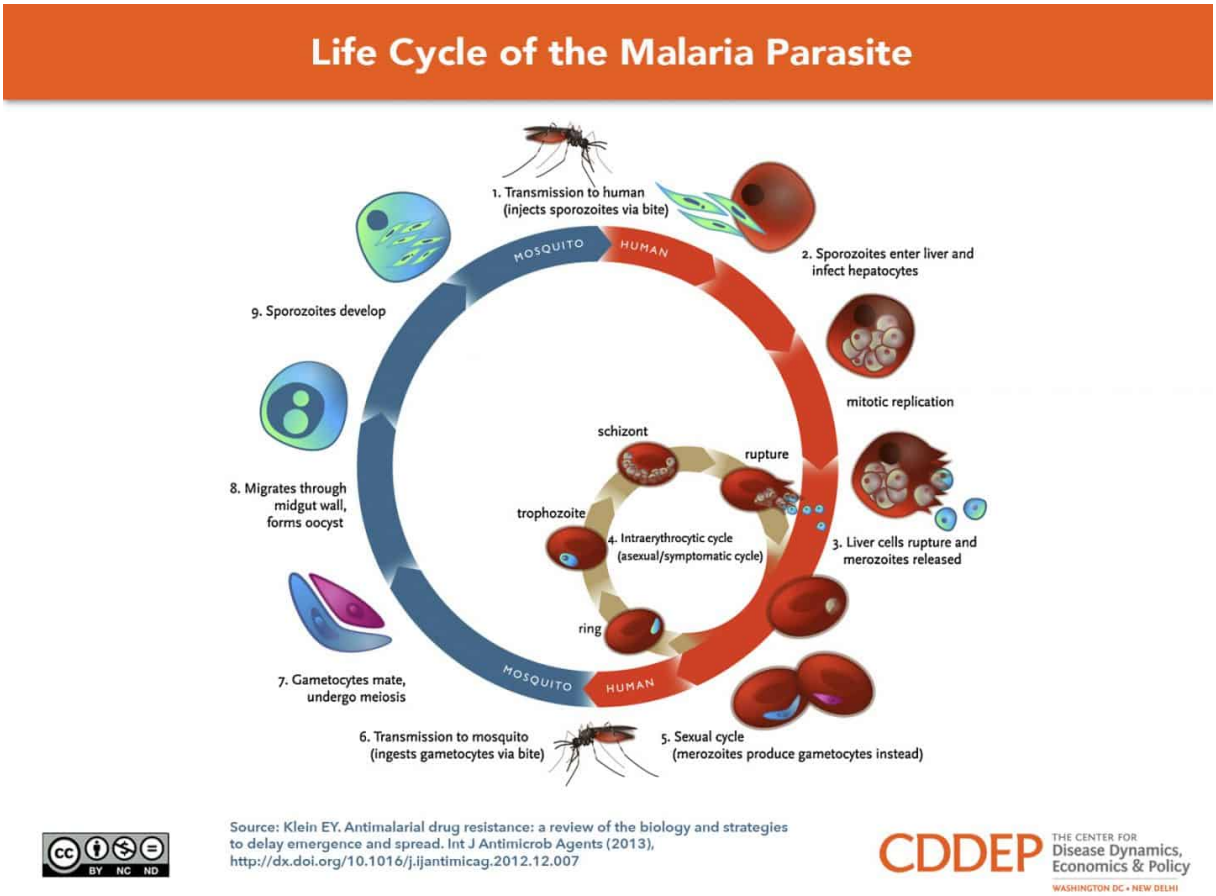


Figure 1: The life cycle of the Plasmodium parasite. Picture was taken from CDDEP (Disease Dynamics, Economics & Policy) https://cddep.org/tool/life_cycle_malaria_parasite/malaria-life-cycle_4/.

1.2 History:

This lethal infectious disease has been around for quite a while. Malaria is believed to have its starting point in Mesopotamia. This because of the crowded population and fertile breeding grounds for mosquitoes. The word malaria comes from the Latin language and means bad air because of the people's recurring fevers, rough fume, and swampy smell. During the time of colonization of African countries, the rate of malaria in European countries increased.

The first effective treatment for malaria came from the *cinchona* tree bark in the 17th century, containing quinine. This method was utilized for more than 150 years, where the bark was attained as a powder. To get the quinine in its purest form, the French chemists Pierre Pelletier and Joseph Caventun managed to extract the quinine from the bark for clinical purposes and made malaria the first disease to be treated by a pure chemical compound. Because of this, the demand for the *Cinchona* trees increased, and many European countries

attempted to plant the *cinchona* tree. Later, in the 1930s, a German researcher named H. Andersag synthesized resochin, which later became known as chloroquine, **CQ**. The synthetic antimalarial drug that has been the most successful is chloroquine. It is safe, inexpensive, and greatly efficacious. However, plasmodial resistance to chloroquine is restraining its viability. Initially, chloroquine was not utilized; therefore, it was conjectured not to be safe for clinical use, yet after some time, studies showed it to be unharmful at therapeutic levels. In 1943, the drug progressed to clinical trials and promptly became prominent due to its efficacy and low risk of side effects [2].

Yet another essential antimalarial is Artemisinin. This compound was discovered by a Chinese research group led by Youyou Tu. An extract from *Artemisia annua* is an herbal medicine that has been to medicate fevers in China for decades. Most modern malaria therapies include the artemisinin derivate. However, it was not accessible until the 1980s because of the political differences between the east and the west. In 2015, Youyou Tu was acknowledged for her discovery and shared the Nobel Prize in Physiology or Medicine [1].

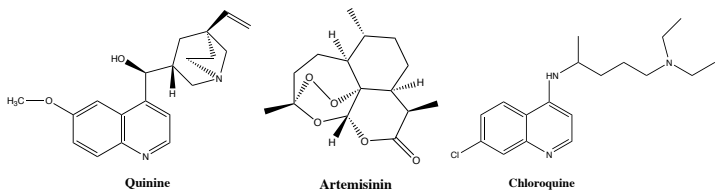


Figure 2: Structures of Quinine, Artemisinin and Chloroquine.

1.3 Hemozoin formation:

All four species of *Plasmodium* parasites that affect the human host crystalline compound called hemozoin during the heme detoxification process. The parasite *Plasmodium Falciparum* consumes up to 80% of its host cell hemoglobin during intraerythrocytic asexual reproduction [8]. Free heme, which gets released in the proteolytic process of hemoglobin, is toxic for the malaria parasite. It is precisely the α-hematin (ferriprotoporphyrin IX, Fe(III PPIX) that is harmful to the parasite. The parasite converts the heme monomer into inert biocrystals called hemozoin, which is chemically identical to synthetic β-hematin, a molecule with paramagnetic properties. Studies on the formation of hemozoin can be divided into two categories. One is under non-biological conditions, and the other is focused on studying the formation of β-hematin in the presence of biological material, either in the form of trophozoite extracts, histidine-rich protein (HRP), or lipids [9].

2 Medicinal organometallic chemistry

2.1 Introduction:

Bio-organometallic chemistry is a new area of research that introduces organometallic chemistry to both medicine and biology. Bio-organometallic chemistry is defined as the study of biologically active molecules that contain one carbon bonded directly to metal. Over the years, this field has seen significant growth.

Ferroquine is a bio-organometallic molecule. It is an amalgamation of a ferrocene core between two amine nitrogens in the sidelong side chains of chloroquine. In 1994, ferroquine was first synthesized and was, as of that time, distinguished as a lead compound for drug development [2]. Ferroquine is also able to overcome chloroquine resistance as it is distinctly active against both chloroquine-sensitive and chloroquine-resistant varieties of *P. falciparum*. Ferroquine has a strong activity against *P. falciparum* that emerges from a combination of factors. The mechanism for ferroquine diversifies from other 4-aminoquinolines, which leads to a more significant accumulation in the digestive vacuole. Ferroquine inhibits β-hematin formation more firmly than chloroquine, indicating that inhibition of hemozoin formation also is essential for ferroquine.

2.2 Quinoline Chemistry:

Quinoline-based antimalarials operate by accumulating in the digestive vacuole. In the digestive vacuole, they form complexes with hematin/Fe(III)PPIX to obstruct its conversion to hemozoin. Chloroquine enters the digestive vacuole in its neutral form. Inside the vacuole, the acidic environment causes protonation of the quinoline nitrogen. However, the protonation now prohibits the positively charged nitrogen from leaving. Thus this leads to an accumulation of the drug a process also described as "pH-trapping." The drug constructs a complex with the hematin inside the vacuole, mainly through π-π interactions [2]. By way of acknowledging the structure-activity relationship studies on chloroquine, it has been ascertained that for a quinoline to act efficaciously as an antimalarial, it has to:

i) Be capable of forming a stable complex with Fe(III)PPIX.

ii) Be able to inhibit the formation of β-hematin/hemozoin.

iii) Be able to contain a basic side to sustain accumulation inside the digestive vacuole.

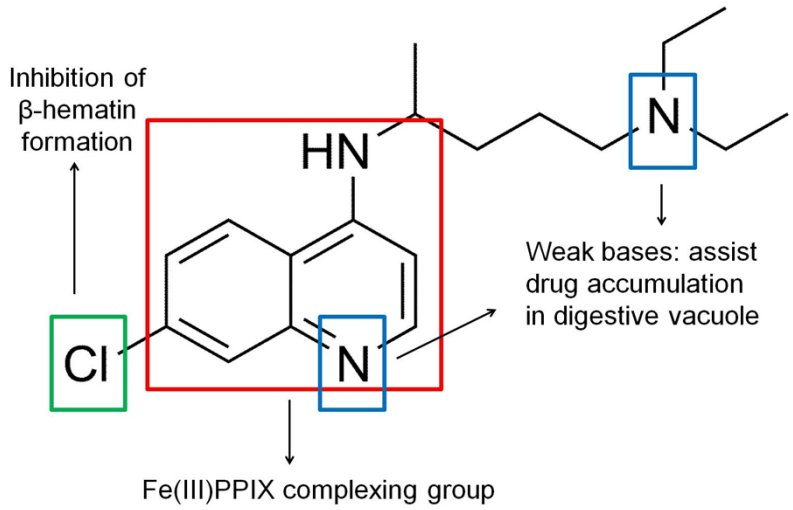


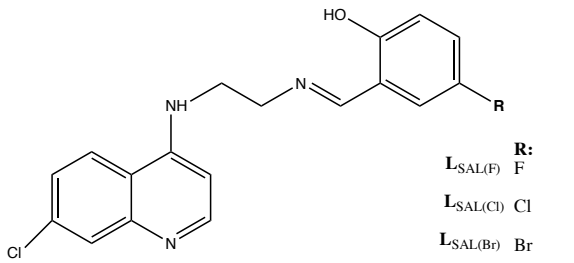
Figure 3: A suggested structure-activity correlation in chloroquine. J. Med. Chem. 2000, 43, 2, 283–291 Publication Date: December 31, 1999 https://doi.org/10.1021/jm990437l.

Chloroquine achieves all these aspects. The 4-aminoquinoline core is pivotal for π-π stacking with Fe(III)PPIX to occur. When carbon replaced the 4-amino nitrogen, it ensued in the weak binding of Fe(III)PPIX, including weak β-hematin inhibition. Furthermore, 2- and 4-aminoquinolines result in strong complexes with Fe(III)PPIX. The 7-chloro group on the chloroquine is an essential feature for inhibition of the β-hematin formation. Studies of chlorine, bromine, and iodine in the 7-position showed high antimalarial activity. The group in the 7-position is required to be strongly lipophilic and electron-withdrawing. Quinolines with 6-fluoro substitution have an inadequate activity analogous to 6-chloro derivatives. Moreover, synthesis of 7-fluoro substitution proved to be futile due to the quinolone undergoing a nucleophilic aromatic substitution efficiently in the existence of amines [15]. A compound where the 7-chloro-4-aminoquinoline is absent of a side chain or has a shorter alkyl chain finishing in a hydroxyl group has a lower antimalarial activity than a compound with a terminal amine. Both short (2-3 carbon) and long carbon (10-12 carbon) side chains correlated to chloroquine have shown great success for chloroquine resistance [15].

3 Results and discussion

3.1 Introduction:

This project is a continuation of the work concluded by Erik Ekengard (2015) and Lotta Glans (2012), who composed their doctoral theses on this study. Both synthesized salicylaldimine ligands and metal precursors. The half-sandwich metal complexes proposed and synthesized by Lotta Glans were complexes of ruthenium, chromium, osmium, manganese, and rhenium. Furthermore, an evaluation of the antimalarial activity was done on the different metal complexes. The ruthenium metal complex contains a $[M(p\text{-cymene})Cl]^+$ moiety with N^O- and N^N-coordinating ligands connected with a 4-aminoquinoline moiety, which is relevant to this project [1]. Moreover, the complex activity is eight more times higher than the free ligand $HL_{SAL(H)}$. Erik Ekengard synthesized eight salicylaldimine-based ligands $\mathbf{HL}_{SAL(F)}$, $\mathbf{HL}_{SAL(Cl)}$, $\mathbf{HL}_{SAL(Br)}$, $\mathbf{HL}_{SAL(I)}$, $\mathbf{HL}_{SAL(NO2)}$, $\mathbf{HL}_{SAL(OMe)}$ and $\mathbf{HL}_{SAL(t\text{-}Bu)}$ and $\mathbf{HL}_{SAL(di\text{-}t\text{-}Bu)}$. Subsequently, the $[(L_{SAL(*)})Ru(p\text{-cymene})Cl]$, $[(L_{SAL(*)})Os(p\text{-cymene})Cl]$, $[Rh(Cp^*)Cl]^+$ and $[Ir(Cp^*)Cl]^+$ complexes were synthesized with the above mentioned ligands. Moreover, the ligands showed to be reasonably effective against chloroquine-sensitive parasites. The rhodium and iridium complexes, also directly related to this project, showed an improved performance relative to the analogous ruthenium complexes. The iridium complexes were less active than the rhodium congeners. To conclude, none of the metal complexes managed to conquer chloroquine resistance.



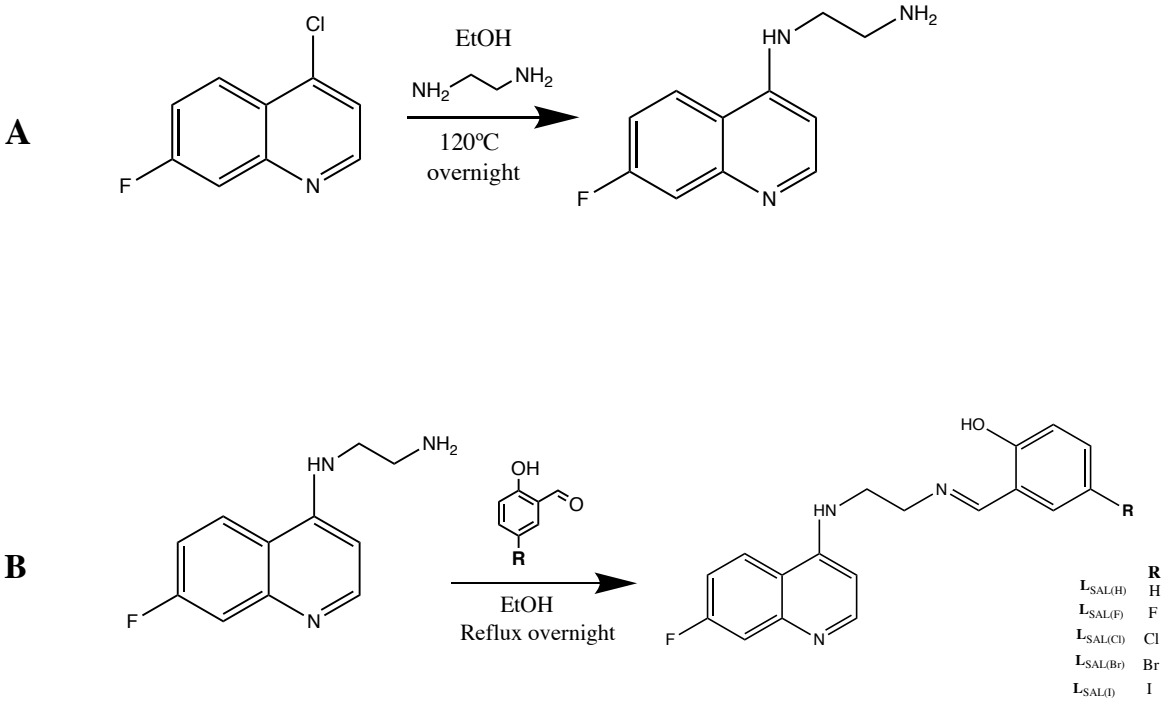
	R:
$\mathbf{L}_{SAL(F)}$	F
$\mathbf{L}_{SAL(Cl)}$	Cl
$\mathbf{L}_{SAL(Br)}$	Br
$\mathbf{L}_{SAL(I)}$	I
$\mathbf{L}_{SAL(NO2)}$	NO_2
$\mathbf{L}_{SAL(OMe)}$	OMe
$\mathbf{L}_{SAL(t\text{-}Bu)}$	t-Bu
$\mathbf{L}_{SAL(di\text{-}t\text{-}Bu)}$	di-t-Bu

Scheme 1. *Synthesis of salicylaldimine ligands* $\boldsymbol{L}_{SAL(F)}$, $\boldsymbol{L}_{SAL(Cl)}$, $\boldsymbol{L}_{SAL(Br)}$, $\boldsymbol{L}_{SAL(I)}$, *and* $\boldsymbol{L}_{SAL(NO2)}$. $\boldsymbol{L}_{SAL(OMe)}$, $\boldsymbol{L}_{SAL(t\text{-}Bu)}$, $\boldsymbol{L}_{SAL(di\text{-}t\text{-}Bu)}$ *by Erik Ekengren.*

3.2 Ligands:

Five ligands in total were synthesized and used for further analysis. $L_{SAL(H)}$, $L_{SAL(Br)}$, $L_{SAL(F)}$, $L_{SAL(I)}$, $L_{SAL(Cl)}$ (Scheme 1). The starting material for these ligands was synthesized from 4-chloro-7-fluoroquinoline and ethylenediamine, generating N1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine (reaction A, Scheme 1). The essence of a correct temperature for this first reaction with 4-chloro-7-fluoroquinoline and ethylenediamine is essential. It is a nucleophilic substitution reaction. A temperature higher than 120℃ will turn the solution into a brown viscous liquid, which also gives a meager yield. The low yield may also be due to the position of the fluorine. The synthesis of 7-fluoro substitution proved to be more difficult due to the 4-chloro-7-quinoline potentially undergoing a nucleophilic aromatic substitution at the fluoro position in the presence of amines. The method developed by Yearick *et al.* [17] where ethanol is not necessary was attempted. A temperature of 130℃ was used and, instead of overnight refluxing, the solution was refluxed in ethanol and ethylenediamine for approximately 6 hours. Nevertheless, similar complications occurred with the starting material not entirely dissolving in dichloromethane. The conclusion was made that the temperature plays a vital role along with a ratio of (1:1) for ethanol and ethylenediamine. Following this method led to a successful reaction; thus, no rapid drip or visible boiling was perceived during the reflux. The work-up proposed by Katti *et al.* [16]. was utilized and found to work effectively. The next step in the syntheses of the different ligands is a Schiff base condensation on of N^1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine condensed with salicylaldehyde in an appropriate amount of ethanol resulting in $HL_{SAL(*)}$-derivatives (Reaction B, Scheme 1). The Schiff bases being formed were insensitive to water; the hydrogen bonding locks the imine in a conformation unfavorable for a hydrolytic attack by water on the imine [1]. Therefore, no precautions were taken for preserving dry conditions. However, pure ligands could not be obtained. Thus a sharp singlet between 12 and 10 ppm in the 1H NMR spectrum showed the appearance of the aldehyde proton. The work-up for the reaction consisted of evaporating the solution under vacuum after dissolving the crude product in dichloromethane and drying the solution over $MgSO_4$, filtration of the mixture, and evaporating the solution to obtain the $L_{SAL(*)}$ ligands. However, the reactions to produce $L_{SAL(Cl)}$, $L_{SAL(Br)}$, and $L_{SAL(I)}$ occurred differently after refluxing in ethanol, precipitation took place when the solutions were cooled to room temperature. After this, the solutions were put in the freezer (-20 ºC) for further precipitation. The precipitation was then isolated via filtration and washed with 2-3 mL of ethanol. However, no crystallization occurred for any of

the ligands. Instead, a cotton-like yellow powder was formed. According to the ^{1}H NMR spectra, N^{1}-(7-fluoroquinolin-4-yl)ethane-1,2-diamine had not reacted with salicylaldehyde to make the ligands **HL**$_{SAL(H)}$, **HL**$_{SAL(F)}$, **HL**$_{SAL(Cl),}$ and **HL**$_{SAL(I)}$. No hydrogen signals were detected where they are supposed to be in the predicted ^{1}H NMR. This can be because the first reaction is both sensitive and impure, affecting the second reaction.

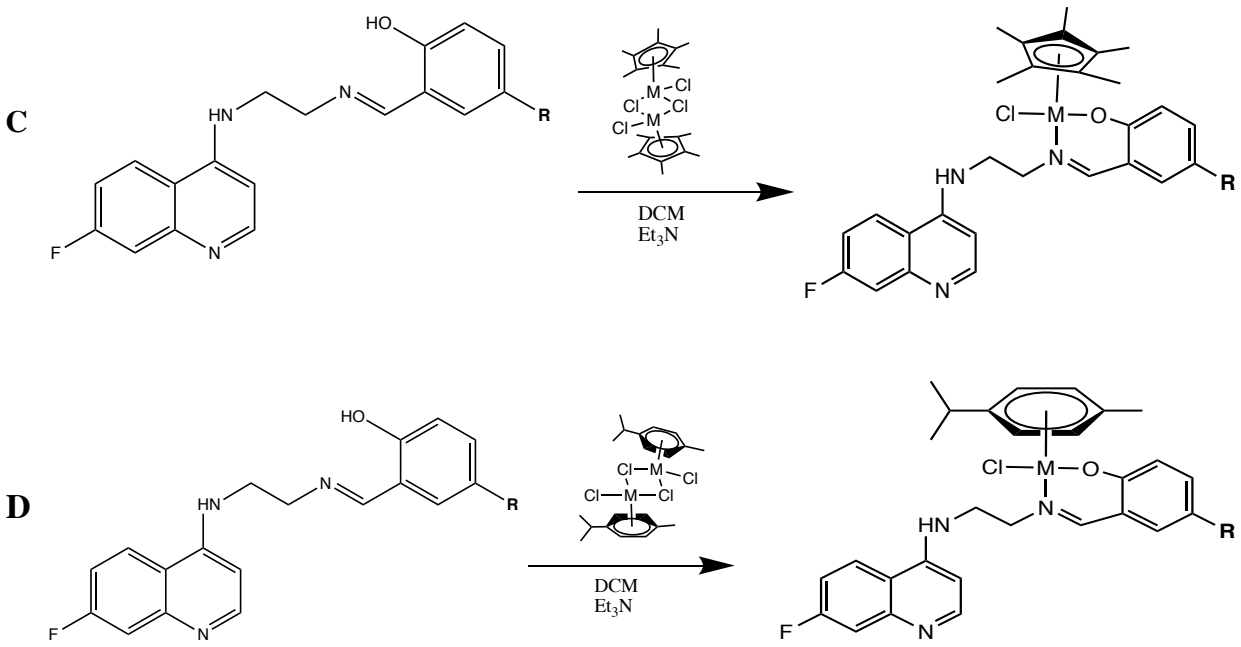


Scheme 1. *A.) Synthesis of N^{1}-(7-fluoroquinolin-4-yl)ethane-1,2-diamine. B.) synthesis of salicylaldimine ligands* ***L***$_{SAL(H),}$ ***L***$_{SAL(F),}$ ***L***$_{SAL(Cl),}$ ***L***$_{SAL(Br),}$ *and* ***L***$_{SAL(I)}$.

3.3 Metal complexes Ruthenium, Iridium, Rhodium:

In the final step, the metal complexes were synthesized by following Erik Ekengard's experimental procedure [14] with. The different salicylaldimine ligand derivatives and the metal dimers [Ir(Cp*)Cl$_2$]$_2$, [Rh(Cp*)Cl$_2$]$_2$ and [Ru(*p*-cymene)Cl$_2$]$_2$. Furthermore, following the procedure, a ratio of 1:2:3 was used of the metal dimer:**L**$_{SAL(*)}$:triethylamine. All of the metal complexes [Ir(L$_{SAL(*)}$)(Cp*)Cl], [Rh(L$_{SAL(*)}$)(Cp*)Cl] and [Ru(L$_{SAL(*)}$)(*p*-cymene)Cl] were synthesized by a pre-equilibration of the specific salicylaldimine ligand in dichloromethane and triethylamine under an ambient temperature and under nitrogen atmosphere until the mixture became homogeneous. This was followed by immerision into an

acetone dry ice bath to cool the reaction. This step is significant since the reaction can lead to decomposition if not cooled to an adequate temperature. After adding the metal dimer, the reaction was left to stir overnight at an ambient temperature and under an inert atmosphere. A reccurring problem with the metal complexes was [NEt_3H]Cl impurities in various metal complexes; thus, the measured yield exceeded 100%. To regulate this issue, celite filtration was considered to remove the fine solids. The [RhCp*($L_{SAL(H)}$)Cl] reaction was purified by column chromatography on silica with a solution of dichloromethane/methanol (9:1 v/v) to afford a purer product of [RhCp*($L_{SAL(H)}$)Cl]. Moreover, crystallization by diffusion of solvents was done in attempts to grow crystals. Since the complex is soluble in dry ether, it was utilized for crystallization. The formation of microcrystals in less than two hours was observed. The crystals were examined under the microscope but were not sufficiently large for crystallographic studies.



Scheme 2. *Syntheses of half-sandwich complexes. Metals: Ir Rh Ru, Ligands: H, F, Cl, Br, I*
C.) Syntheses of [Ir(Cp)(**L**$_{SAL(*)}$)Cl] and [Rh(Cp*)(**L**$_{SAL(*)}$)Cl]. D.) Synthesis of [Ru(ρ-cymene)(**L**$_{SAL(*)}$)Cl].*

3.4 Experimental:

N^1 - (7-fluoroquinolin-4-yl)ethane-1,2-diamine: An overnight reflux occurred, with (200 mg, 1.101 mmol) of 4-chloro-7-fluoroquinoline and (0.736 mL, 10.98 mmol) of ethane-1,2-diamine in 0.736 mL of ethanol at 110 ℃. In the work-up stages, the solvent was first dissolved in dichloromethane (DCM). Later the solution was washed with 5 M $NaHCO_3$, subsequently with water, and then brine. The drying agent anhydrous Na_2SO_4 was used to dry the organic layer, to then be filtered. Furthermore, the solution was evaporated and then dried under a vacuum. The product was obtained as a white powder (158 mg, 70 %).
^{1}H NMR (400 MHz, DMSO) δ 8.43 – 8.28 (m, 5H), 8.27 – 8.18 (m, 1H), 7.55 (s, 1H), 7.45 (dd, J = 10.9, 2.8 Hz, 3H), 7.33 (td, J = 8.7, 2.7 Hz, 3H), 7.23 (s, 2H), 6.81 (s, 1H), 6.47 (d, J = 5.4 Hz, 3H), 3.27 (t, J = 5.5 Hz, 3H), 2.84 (t, J = 6.4 Hz, 4H), 0.06 (d, J = 5.5 Hz, 1H), -0.06 (s, 1H).

N^1 -(7-(trifluoromethyl)quinolin-4-yl)ethane-1,2-diamine: An overnight reflux was carried out, with (500 mg, 2.159 mmol) of 4-chloro-7-(trifluoromethyl)quinoline and (1.45 mL, 22.44 mmol) of ethane-1,2-diamine in 1.45 mL of ethanol at 110 ℃. In the work-up, the mixture was first dissolved in dichloromethane (DCM). Later the solution was washed with 5 M $NaHCO_3$, subsequently with water, and then brine. The drying agent anhydrous Na_2SO_4 was used to dry the organic layer, to then be filtered. The solution was evaporated and then dried under a vacuum. The product was obtained as a yellow powder (462 mg, 84 %).
^{1}H NMR (400 MHz, DMSO) δ 8.53 – 8.46 (m, 4H), 8.08 (d, J = 1.9 Hz, 2H), 7.68 (dd, J = 8.8, 2.0 Hz, 2H), 7.39 (t, J = 5.1 Hz, 2H), 6.61 (d, J = 5.5 Hz, 2H), 3.29 (q, J = 6.0 Hz, 5H), 2.84 (d, J = 6.5 Hz, 3H).

(*E*)-2-(((2-((7-fluoroquinolin-4-yl)amino)ethyl)imino)methyl)phenol ($L_{SAL(H)}$): N^1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine (38 mg, 0.185 mmol) and salicylaldehyde (19.7 µL, 0.189 mmol) was added to 10 mL of ethanol. After the addition, the mixture was let to reflux overnight. The solvent was evaporated, dissolved in dichloromethane, and the organic layer was then dried with anhydrous Na_2SO_4. After using the drying agent, the mixture was filtered and then evaporated to be dried over vacuum overnight. The product was obtained as a yellow powder (49 mg, 85%). Numerous insignificant peaks were found in the 1 H NMR spectrum, hard to detect relevant peaks, impure sample.

IR ν_{max}/cm^{-1} 3406w (*O*-H), 3212w, 3052w, 2963w, 2918w, 2851w, 2717w, 2635w, 1576s (N=C), 1494m (7-chloroquinoline), 1453m, 1416m, 1371m, 1259m, 1148m, 1088s, 1017s, 894s, 857s, 797s, 738m

(*E*)-4-fluoro-2-(((2-((7-fluoroquinolin-4-yl)amino)ethyl)imino)methyl)phenol (L$_{SAL(F)}$): N^1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine (121 mg, 0.6 mmol) and 5-fluorosalicylaldehyde (82.7 mg, 0.6 mmol) was added to 10 mL of ethanol. After the addition, the mixture was let to reflux overnight. The solvent was evaporated, dissolved in dichloromethane, and the organic layer was then dried with anhydrous Na_2SO_4. After the use of the drying agent, the solvent was evaporated and the residue was dried over vacuum overnight. The product was obtained as a yellow powder (121 mg, 62 %). Numerous insignificant peaks were found in the 1 H NMR spectrum - hard to detect relevant peaks, impure sample.

(*E*)-4-chloro-2-(((2-((7-fluoroquinolin-4-yl)amino)ethyl)imino)methyl)phenol (L$_{SAL(Cl)}$): N^1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine (60 mg, 0.29 mmol) and 5-chlorosalicylaldehyde (45.76 mg, 0.29 mmol) were added to 10 mL of ethanol. After the addition, the mixture was let to reflux overnight. The reaction was cooled to room temperature, and precipitation occurred. The solution was placed in the freezer (-20 ºC) overnight. The precipitate was filtered off and washed with (2-3 mL) ethanol. The solvent was evaporated, dissolved in dichloromethane, and the organic layer was then dried with anhydrous Na_2SO_4. After using the drying agent, the mixture was filtered and then evaporated to be dried over vacuum overnight. The product was attained as a yellow powder and paper-thin crystalline solids (58 mg, 57 %). Numerous insignificant peaks were found in the 1 H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3824w (*O*-H), 1736m (C=O), 1621m (N=C), 1558m (7-chloroquinoline), 1476m, 1364s, 1259m, 1215m, 1088m, 1032m

(*E*)-4-bromo-2-(((2-((7-fluoroquinolin-4-yl)amino)ethyl)imino)methyl)phenol (L$_{SAL(Br)}$): N^1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine (158 mg, 0.768 mmol) and

5-bromosalicylaldehyde (154.76 mg, 0.768 mmol) were added to 20 mL of ethanol. After the addition, the mixture was let to reflux overnight. The reaction was cooled to room temperature, and precipitation occurred. The solution was placed in the freezer (-20 ºC) overnight. The precipitate was filtered and washed with (2-3 mL) ethanol. The solvent was evaporated, dissolved in dichloromethane, and the organic layer was then dried with anhydrous Na_2SO_4. After using the drying agent, the mixture was filtered and then evaporated to be dried over vacuum overnight. The product was obtained as a yellow microcrystalline powder (154 mg, 51 %). δ ^{1}H NMR (400 MHz, DMSO) 10.95 (s, 1H), 9.87 (d, J = 0.7 Hz, 1H), 8.37 – 8.29 (m, 1H), 8.23 (s, 1H), 7.76 – 7.68 (m, 1H), 7.63 (dd, J = 8.9, 2.5 Hz, 1H), 7.44 – 7.26 (m, 3H), 6.97 – 6.80 (m, 1H), 6.82 – 6.71 (m, 1H), 5.64 (s, 1H), 4.12 (t, J = 5.8 Hz, 1H), 3.90 (t, J = 5.9 Hz, 1H), 3.80 – 3.57 (m, 4H), 1.29 (t, J = 7.1 Hz, 7H), 0.09 (s, 1H). IR: ν_{max}/cm^{-1} 1736m, 1613m (N=C), 1558m (7-chloroquinoline), 1472w, 1360m, 1215m, 1185w, 1077w, 1028m, 894w, 820s, 689w.

(*E*)-2-(((2-((7-fluoroquinolin-4-yl)amino)ethyl)imino)methyl)-4-iodophenol (L$_{SAL(I)}$): N1-(7-fluoroquinolin-4-yl)ethane-1,2-diamine (43 mg, 0.21 mmol) and 5-iodosalicylaldehyde (49.5 mg, 0.21 mmol) were added to 10 mL of ethanol. After the addition, the mixture was let to reflux overnight. The reaction was cooled to room temperature, and precipitation occurred. The solution was placed in the freezer (-20 ºC) overnight. The precipitate was filtered and washed with (2-3 mL) ethanol. The solvent was evaporated, dissolved in dichloromethane, and the organic layer was then dried with anhydrous Na2SO4. After using the drying agent, the mixture was filtered and then evaporated to be dried over vacuum overnight. The product was obtained as a yellow microcrystalline powder (50 mg, 63 %). Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3905w (*O*-H), 3805w (*O*-H), 2083w, 2053w, 1986w, 1904w, 1774w, 1628m (N=C), 1595m (7-chloroquinoline), 1561m (7-chloroquinoline), 1472m, 1390m, 1360m, 1274m, 1218m, 1185m, 1129m, 1073m, 1032m, 980w, 902s, 823s, 682w

(E)-4-fluoro-2-(((2-((7-(trifluoromethyl)quinolin-4-yl)amino)ethyl)imino) methyl)phenol (L$_{SAL(F)}$): 4-chloro-7-(trifluoromethyl)quinoline (60 mg, 0.4 mmol) and 5-fluorosalicylaldehyde (32.93 mg, 0.4 mmol) were added to 10 mL of ethanol. After the

addition, the mixture was let to reflux overnight. The solvent was evaporated, dissolved in dichloromethane, and the organic layer was then dried with anhydrous Na_2SO_4. After using the drying agent, the mixture was filtered and then evaporated to be dried over vacuum overnight. The product was obtained as a yellow powder (75 mg, 84%).
^{1}H NMR (400 MHz, DMSO) δ 8.52 (d, J = 5.2 Hz, 2H), 8.45 (d, J = 8.8 Hz, 1H), 8.09 (t, J = 1.5 Hz, 1H), 7.70 (dd, J = 8.8, 2.1 Hz, 1H), 7.63 (t, J = 5.7 Hz, 1H), 7.31 (ddd, J = 17.1, 8.9, 3.2 Hz, 1H), 7.18 (td, J = 8.7, 3.2 Hz, 1H), 6.89 (ddd, J = 9.0, 4.6, 1.8 Hz, 1H), 6.73 (d, J = 5.5 Hz, 1H), 3.96 – 3.88 (m, 2H), 3.68 (q, J = 5.9 Hz, 2H).
IR: ν_{max}/cm^{-1} 3798w, 3731w, 3160br (*O*-H), 3078w (*O*-H), 2847w, 2713w, 2542w, 2389w, 2355w, 2307w, 2273w, 2206w, 2132w, 2102w, 2012w, 1941w, 1897w, 1863w, 1766m, 1636m (N=C), 1572m (7-chloroquinoline), 1550m (7-chloroquinoline), 1494w, 1326s, 1271m, 1196w, 1159s, 1114s, 1069w, 987m, 909m, 849m, 782m, 738m, 678m.

(*E*)-4-chloro-2-(((2-((7-(trifluoromethyl)quinolin-4-yl)amino)ethyl)imino) methyl)phenol ($L_{SAL(Cl)}$): 4-chloro-7-(trifluoromethyl)quinoline (60 mg, 0.4 mmol) and 5-chlorosalicylaldehyde (36.8 mg, 0.4 mmol) were added to 10 mL of ethanol. After the addition, the mixture was let to reflux overnight. The solvent was evaporated, dissolved in dichloromethane, and the organic layer was then dried with anhydrous Na_2SO_4. After using the drying agent, the mixture was filtered and then evaporated to be dried over vacuum overnight. The product was obtained as a yellow powder (83 mg, 85 %).
^{1}H NMR (400 MHz, DMSO) δ 13.46 (s, 1H), 8.56 – 8.49 (m, 2H), 8.45 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.70 (dd, J = 8.8, 2.0 Hz, 1H), 7.66 – 7.53 (m, 1H), 7.50 (d, J = 2.7 Hz, 1H), 7.34 (dd, J = 8.8, 2.7 Hz, 1H), 6.89 (d, J = 8.9 Hz, 1H), 6.73 (d, J = 5.5 Hz, 1H), 3.92 (t, J = 5.9 Hz, 2H), 3.68 (q, J = 5.9 Hz, 2H).
IR: ν_{max}/cm^{-1} 3209br (*O*-H), 3075w, 3041w, 2963w, 2616w, 2497w, 1632m (N=C), 1591m (7-chloroquinoline), 1472w, 1375m, 1326m, 1274w, 1222m, 1162w, 1114s, 1058w, 1028w, 969w, 913w, 797s, 697m.

(η5-pentamethylcyclopentadienyl){(N-(2-((2-hydroxyphenyl)methylimino)ethyl)-6-fluoroquinolin-4-amine)}chlororhodium(III) [RhCp*($L_{SAL(H)}$)Cl]: To $L_{SAL(H)}$ (48.0 mg, 154 μmol), triethylamine (32.0 μL, 231 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a

homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, $[Rh(Cp^*)Cl_2]_2$ (47.5 mg, 77 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under a vacuum overnight. The product was obtained as a red powder. The crude product was then purified by column chromatography on silica with a solution of dichloromethane/methanol (9:1 v/v) to afford a purer product of $[RhCp^*(L_{SAL(H)})Cl]$ Yield: 15.34 mg (17 Numerous insignificant peaks were found in the ^1H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3902w, 3805w, 3749w, 3589w, 2970br (*O*-H), 2922w, 1736s, 1528m (7-chloroquinoline), 1438m, 1371m, 1025s

(η5-pentamethylcyclopentadienyl){(N-(2-((5-fluoro-2-hydroxyphenyl) methylimino)ethyl)-6-fluoroquinolin-4-amine)}chlororhodium(III), [RhCp*($L_{SAL(F)}$)Cl]: To $L_{SAL(F)}$ (33.05 mg, 100 μmol), triethylamine (20.84 μL, 150 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, $[Rh(Cp^*)Cl_2]_2$ (30.98 mg, 50 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under a vacuum overnight. The product was obtained as a red powder (51 mg, 84 %). Numerous insignificant peaks were found in the ^1H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3395w, 3261w, 2963w, 2922br (*O*-H), 2605w, 2497w, 1625m (N=C), 1587m (7-chloroquinoline), 1543w, 1461m, 1375m, 1289w, 1259m, 1226w, 1144w, 1080m, 1021w, 965w, 872w, 797m, 682w.

(η5-pentamethylcyclopentadienyl){(N-(2-((5-chloro-2-hydroxyphenyl) methylimino)ethyl)-6-flouroquinolin-4-amine)}chlororhodium(III), [RhCp*($L_{SAL(Cl)}$)Cl]: To $L_{SAL(Cl)}$ (29 mg, 84 μmol), triethylamine (17.42 μL, 126 μmol) and 15 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, $[Rh(Cp^*)Cl_2]_2$ (25.89 mg, 42 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a red color and was stirred

overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under a vacuum overnight. The product was obtained as a red powder (65 mg, 124 %). The inorganic impurities were diminished by celite filtration (35 mg, 67%). Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3906w, 3615w, 3444w, 3261br (*O*-H), 3067w, 2922br (*O*-H), 2601m , 2530m, 2497m, 1617s (7-chloroquinoline), 1580 (7-chloroquinoline), 1543 (7-chloroquinoline), 1457s, 1375m, 1312w, 1226m, 1170m, 1125w, 1095w, 1021m, 961w, 868m, 820w, 764w, 700w.

(η5-pentamethylcyclopentadienyl){(N-(2-((5-fluoro-2-hydroxyphenyl) methylimino)ethyl)-6-fluoroquinolin-4-amine)}chlororhodium(III), [RhCp*($L_{SAL(F)}$)Cl]: To $L_{SAL(F)}$ (50 mg, 132 µmol), triethylamine (27.39 µL, 198 µmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 ℃). After that, $[Rh(Cp^*)Cl_2]_2$ (40.71 mg, 66 µmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under a vacuum overnight. The product was obtained as a red powder (94 mg, 109 %).

1H NMR (400 MHz, DMSO) δ 8.52 (dd, J = 5.5, 3.5 Hz, 2H), 8.44 (t, J = 8.6 Hz, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.73 – 7.63 (m, 1H), 7.56 (s, 1H), 7.06 (td, J = 8.8, 3.4 Hz, 1H), 6.94 – 6.84 (m, 2H), 6.77 – 6.66 (m, 1H), 5.76 (s, 1H), 4.21 (s, 2H), 3.96 – 3.88 (m, 1H), 3.68 (d, J = 6.0 Hz, 1H), 2.91 (s, 10H), 1.64 (s, 7H), 1.53 (s, 1H), 1.48 (s, 13H), 1.11 (s, 11H) IR: ν_{max}/cm^{-1} 3567w, 3406w, 3242w, 2966w, 2925br (*O*-H), 2609m, 2534m, 2497w, 1625m (C=N), 1591m (7-chloroquinoline), 1543w (7-chloroquinoline), 1461m, 1375m, 1326m, 1263w, 1203w, 1118m, 1069m, 1021m, 905w, 805s, 685w

(η5-pentamethylcyclopentadienyl){(N-(2-((5-chloro-2-hydroxyphenyl) methylimino)ethyl)-6-flouroquinolin-4-amine)}chlororhodium(III), [RhCp*($L_{SAL(Cl)}$)Cl]: To $L_{SAL(Cl)}$ (50 mg, 126µmol), triethylamine (26.25 µL, 189 µmol) and 15 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an

acetone-dry ice bath (-78 ℃). After that, $[Rh(Cp^*)Cl_2]_2$ (39.027 mg, 63 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under a vacuum overnight. The product was obtained as a red powder (45 mg, 85 %). The inorganic impurities were diminished by celite filtration (110 mg, 130%).
δ ^{1}H NMR (400 MHz, DMSO) 8.53 (d, J = 5.4 Hz, 1H), 8.43 (d, J = 8.9 Hz, 1H), 8.11 – 8.01 (m, 2H), 7.66 (dd, J = 8.9, 2.0 Hz, 1H), 7.59 (s, 1H), 7.18 – 7.10 (m, 2H), 6.92 (d, J = 5.5 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 5.76 (s, 1H), 4.20 (s, 2H), 3.98 (s, 1H), 3.05 (d, J = 7.5 Hz, 6H), 1.63 (s, 1H), 1.48 (s, 14H), 1.18 (t, J = 7.3 Hz, 10H), -0.06 (s, 1H)
IR: ν_{max}/cm^{-1} 3276w, 3048w, 2963br (*O*-H), 2922w, 2739w, 2605m, 2530w, 2497w, 1617m (N=C), 1587m (7-chloroquinoline), 1543w, 1457m, 1375m, 1323w, 1259w, 1159s, 1118s, 1069w, 1021s, 902w, 797s, 704w.

(η5-pentamethylcyclopentadienyl){(N-(2-((5-bromo-2-hydroxyphenyl) methylimino)ethyl)-6-flouroquinolin-4-amine)}chlororhodium(III) [RhCp*($L_{SAL(Br)}$)Cl]: To $L_{SAL(Br)}$ (29 mg, 74 μmol), triethylamine (15.43 μL, 111 μmol) and 15 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 ℃). After that, $[Rh(Cp^*)Cl_2]_2$ (22.94mg, 37 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as a red powder (43 mg, 87 %). Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3447w, 3261w, 2963m (*O*-H), 2922w, 2858w, 2609w, 2497w, 1673w (C=N), 1621m, 1587w (7-chloroquinoline), 1558w (7-chloroquinoline), 1520m, 1457m, 1375w, 1293m, 1259w, 1230w, 1170w, 1080m, 1013s, 868s, 793w, 700w.

(η6-p-Cymene)(N-(2-((5-chloro-2-hydroxyphenyl)methylimino)-ethyl)-6-fluoroquinolin-4-amine)chlororuthenium(II), [Ru(ρ-Cymene)($L_{SAL(H)}$)Cl]: To $L_{SAL(H)}$ (56 mg, 180 μmol), triethylamine (37.35 μL, 270 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to

achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, $[Ru(\rho\text{-Cymene})Cl_2]_2$ (55.01 mg, 90 μmol) were added in 2 mL dichloromethane to the cooled mixture. The solution obtained a red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as a brown powder (96 mg, 92 %). Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3902w, 3824w, 3749w, 2966br (*O*-H), 2601w, 2497w, 1736s (C=O), 1587m (C=N), 1543 (7-chloroquinoline), 1468m, 1367s, 1259w, 1226w, 1136w, 1080w, 1032s, 864m, 797w, 674

(η6-p*Cymene*)(N-(2-((5-fluoro-2-hydroxyphenyl)methylimino)-ethyl)-6-chloroquinolin-4-amine)chlororuthenium(II), [Ru(*p*-Cymene)($L_{SAL(F)}$)Cl]: To $L_{SAL(F)}$ (57.5 mg, 174 μmol), triethylamine (36.26 μL, 262 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, $[Ru(p\text{-Cymene})Cl_2]_2$ (53.4 mg, 87 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a dark red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as a brown powder (137 mg, 128 %). The inorganic impurities were diminished by celite filtration (57 mg, 55 %). Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3902w, 3824w, 3749w, 3589w, 3507w, 3276w, 2966br (*O*-H), 2922w, 2605w, 1736m, 1625w, 1587m (7-chloroquinoline), 1543w (7-chloroquinoline), 1457m, 1371s, 1293w, 1259w, 1230m, 1144w, 1080w, 1017s, 864w, 797s, 685w.

(η6-p-Cymene)(N-(2-((5-chloro-2-hydroxyphenyl)methylimino)-ethyl)-6-fluoroquinolin-4-amine)chlororuthenium(II), [Ru(*p*-Cymene)($L_{SAL(Cl)}$)Cl]: To $L_{SAL(Cl)}$ (39.1 mg, 113 μmol), triethylamine (23.42 μL, 169 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, $[Ru(p\text{-Cymene})Cl_2]_2$ (34.5 mg, 56 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a dark red color and was stirred

overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as a brown powder (49 mg, 71 %) . The crude product was then purified by column chromatography on silica with a solution of dichloromethane/methanol (9:1 v/v) to afford a purer product of [Ru(ρ-Cymene)($L_{SAL(Cl)}$)Cl] Yield: 15.34 mg (17%). Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3902w, 3824w, 3749w, 3034w, 2959br (*O*-H), 2925w, 2870w, 2605w, 1736m, 1591m (7-chloroquinoline), 1461m, 1375m, 1323w, 1259m, 1230w, 1174w, 1092m, 1032s, 875w, 801s, 738w, 708w.

(η6-p-Cymene)(N-(2-((5-bromo-2-hydroxyphenyl)methylimino)-ethyl)-6-fluoroquinolin-4-amine)chlororuthenium(II), [Ru(*p*-Cymene)($L_{SAL(Br)}$)Cl]: To **$L_{SAL(Br)}$** (89.0 mg, 228 μmol), triethylamine (47.37 μL, 342 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, [Ru(*p*-Cymene)Cl_2]$_2$ (69.7 mg, 114 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a dark red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as a brown powder (117 mg, 78 %) . Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3283w, 3060w, 2963br (*O*-H), 2929w, 2739w, 2601m, 2497w, 1610m, 1554m (7-chloroquinoline), 1505w, 1461m, 1397m, 1319m, 1259m, 1226w, 1174w, 1088w, 1036m, 868w, 805m, 715m.

(η6-p-Cymene)(N-(2-((5-iodo-2-hydroxyphenyl)methylimino)-ethyl)-6-flouroquinolin-4-amine)chlororuthenium(II), [Ru(*p*-Cymene)($L_{SAL(I)}$)I]: To **$L_{SAL(I)}$** (33.0 mg, 47 μmol), triethylamine (15.68 μL, 70 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 °C). After that, [Ru(*p*-Cymene)Cl_2]$_2$ (23.09 mg, 23 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained a dark red color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as a brown powder (68 mg, 123 %) . The

inorganic impurities were diminished by celite filtration (18 mg, 34 %). Numerous insignificant peaks were found in the ^{1}H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3451w, 3242w, 2959w, 2918br (*O*-H), 2847w, 2497w, 1736w, 1621m (N=C), 1587w (7-chloroquinoline), 1543m, 1461m, 1375w, 1289m, 1259m, 1230w, 1080w, 1017m, 864w, 797s, 685w.

(η5-pentamethylcyclopentadienyl){(N-(2-((2-hydroxyphenyl)methylimino)ethyl)-6-chloroquinolin-4-amine)}chloroiridium(III), [IrCp*($L_{SAL(H)}$)Cl] : To $\mathbf{L}_{SAL(H)}$ (68 mg, 218 μmol), triethylamine (45.36 μL, 327 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 ℃). After that, $[Ir(Cp^*)Cl_2]_2$, (86 mg, 109 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained an orange color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was attained as an orange powder (192 mg, 130%). The inorganic impurities were diminished by celite filtration (105 mg, 71 %). Numerous insignificant peaks were found in the 1 H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3906w, 3805w, 2966w, 2918s (*O*-H), 1736w, 1613w, 1535m (7-chloroquinoline), 1446m, 1375w, 1323w, 1259w, 1226w, 1080w, 1025s, 797s, 752w

(η5-pentamethylcyclopentadienyl){(N-(2-((5-fluoro-2-hydroxyphenyl) methylimino)ethyl)-6-fluoroquinolin-4-amine)}chloroiridium(III), [IrCp*$_{(LSAL(F))}$Cl]: To $\mathbf{L}_{SAL(F)}$ (64 mg, 194 μmol), triethylamine (40.36 μL, 291 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 ℃). After that, $[Ir(Cp^*)Cl_2]_2$ (77.33 mg, 97 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained an orange color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as an orange powder 120 mg, 89%). Numerous insignificant peaks were found in the 1 H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3449w, 3294w, 3063w, 2963br (*O*-H), 2918w, 2739w, 2601w, 2497w, 1617m, 1587m (7-chloroquinoline), 1543w (7-

chloroquinoline), 1461w, 1379w, 1293m, 1259w, 1226w, 1170w, 1144w, 1080w, 1025s, 864w, 797s, 715w.

(η5-pentamethylcyclopentadienyl){(N-(2-((5-chloro-2-hydroxyphenyl) methylimino)ethyl)-6-chloroquinolin-4-amine)}chloroiridium(III), [IrCp*($L_{SAL(Cl)}$)Cl]: To $L_{SAL(Cl)}$ (29 mg, 84 μmol), triethylamine (17.42 μL, 126 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 ℃). After that, $[Ir(Cp^*)Cl_2]_2$ (33.37 mg, 42 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained an orange color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as an orange powder (70 mg, 117%). The inorganic impurities were diminished by celite filtration (20 mg, 60%). Numerous insignificant peaks, hard to detect relevant peaks, impure sample.
IR: ν_{max}/cm^{-1} 3887w, 3298w, 2922br (*O*-H), 2605m, 2530w, 2497m, 1736w, 1587m (7-chloroquinoline), 1558w (7-chloroquinoline), 1457m, 1379w, 1315w, 1226w, 1170, 1077w, 1028s, 797s, 704w.

(η5-pentamethylcyclopentadienyl){(N-(2-((5-bromo-2-hydroxyphenyl) methylimino)ethyl)-6-chloroquinolin-4-amine)}chloroiridium(III), [IrCp*($L_{SAL(Br)}$)Cl]: To $L_{SAL(Br)}$ (29 mg, 74 μmol), triethylamine (15.43 μL, 111 μmol) and 20 mL dichloromethane were added. This solution was then stirred for 30 minutes under an inert atmosphere to achieve a homogeneous mixture. The mixture was cooled in an acetone-dry ice bath (-78 ℃). After that, $[Ir(Cp^*)Cl_2]_2$ (29.57 mg, 37 μmol) was added in 2 mL dichloromethane to the cooled mixture. The solution obtained an orange color and was stirred overnight at an ambient temperature under an inert atmosphere. The solution was evaporated and afterward dried under vacuum overnight. The product was obtained as an orange powder (45 mg, 85%). Numerous insignificant peaks were found in the 1 H NMR spectrum - hard to detect relevant peaks, impure sample. IR: ν_{max}/cm^{-1} 3291w, 2963br (*O*-H), 2922w, 2601w, 2497w, 1617m, 1587m (7-chloroquinoline), 1550w (7-chloroquinoline), 1457m, 1379w, 1289m, 1259m, 1226w, 1170w, 1077m, 1021s, 965w, 864w, 797s, 685w.

4 Conclusion

This study aimed to synthesize fifteen new metal complexes containing N^N chloroquine analog ligands with ruthenium, iridium, and rhodium. Due to 4-chloro-7-fluoroquinoline being a sensitive starting material, the results and 1H NMR, unfortunately, showed no pure complexes. The results of the reactions might have improved if they were carried out under an inert atmosphere. Another starting material, 4-chloro-7-(trifluoromethyl)quinoline, was used as this complex was reliably substituted at the 4-chloro position of the quinoline. The 1H NMR showed pure ligands and pure rhodium metal complexes for 4-chloro-7-(trifluoromethyl)quinoline. Because of time restraint, antimalarial activity on the different complexes not studied.

Populärvetenskaplig sammanfattning

Malaria är en tropisk sjukdom som orsakas av en encellig parasit av släktet *Plasmodium* och sprids till människor via infekterade myggor. Smittan uppstår genom stick från honmyggor av Anopheles-släktet. Efter sticket, tar sig parasiten till levern och sedan till de röda blodkropparna som efter ett tag spricker. Därefter kommer parasiten ut i blodet tillsammans med andra nedbrytningsprodukter vilka är toxiska. Malariainfektionen leder till feber, frossa och kräkningar. Det finns fyra olika arter av Plasmodium-parasiter som smittar människor, vilket är *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae* och *Plasmodium ovale*. Parasiten *P. falciparum* är den dödligaste utav alla; ungefär 20 procent av alla fall smittade med denna parasit leder till döden i avsaknad av behandling. Ett stort problem är att många av malariaparasiterna har uppnått resistens mot de mest effektiva och användbara läkemedlen. Klorokin-, är ett antimalaria-läkemedel som upptäcktes 1934 av Hans Andersag, en tysk forskare. Läkemedlet är effektivt mot den asexuella formen av malariasjukdomen i de röda blödkropparna. Klorokin används då den är billig, effektiv och har relativt milda biverkningar. Detta har lett till en stor förbrukning av läkemedlet, vilket betyder att nästintill alla malariaparasiter har blivit immuna mot klorokin, d v s. att parasiten har råkat muteras på något sätt och härigenom blivit immun mot klorokin. För att resistens inte ska växa fram snabbt, används flera läkemedel samtidigt, då kan andra läkemedel i blandningen döda patogenen ifall resistens uppstår mot ett av läkemedlen. När en läkemedelresistens uppstår kan en kemiskt modifikation av läkemedelsmolekylen vara en enkel lösning för att få fram ett nytt läkemedel. Denna metod har fungerat för klorokin-, bl a med hjälp av att inkludera en metallorganisk sandwich-förening i den molekylära strukturen för klorokin. På detta sätt skapades läkemedlet ferrokin, vilket är mycket effektivt även mot klorokinresistenta malariaparasiter. Sandwich-föreningar är ämnen med en metallatom som är fastbunden till två ringar av kolatomer därpå ligger dessa två ringar plant mot metallatomen. I fallet ferrokin användes järn som metall. Det finns också så kallade till halv-sandwich-föreningar vilket betyder att metallatomen endast är fastbunden till en ring av kolatomer. Detta innebär att flertal ämnen kan binda sig till metallen ty bara ena sidan av metallen är bunden till kolringen. Förut har klorokinliknande halv-sandwichföreningar blivit syntetiserade och istället för en järnatom har rutenium, osmium, rhodium och iridium använts för att se dess förmåga att döda malariaparasiter. Det visade sig att ingen av de ovannämda föreningarna var i synnerhet gynnsam på att döda malariaparasiter mer än de klorokinliknande ämnena utan metaller. I detta projekt användes metallatomerna rutenium, rhodium och iridium i halv-

sandwichföreningar. Istället för en kloratom på den aktiva delen användes en fluoratom för att se dess effektivitet samt vad detta har för någon inflytande på malariaparasiten.

Acknowledgment

Ebbe, Tack så mycket att jag fick äran att göra mitt projekt i din grupp på kemisk fysik. Tack för att jag fick förtroendet att sätta mig in i detta projektet, det har varit ett väldigt lärorikt projekt.

Yong, Thanks for all the helpful advice and help in the lab. I am also grateful for your profound belief in my work.

Hassan och Stefan, tusen tack för eran hjälp i labbet och tack för alla era goda råd.

Linn, Tack för alla roliga stunder i labbet.

5 References

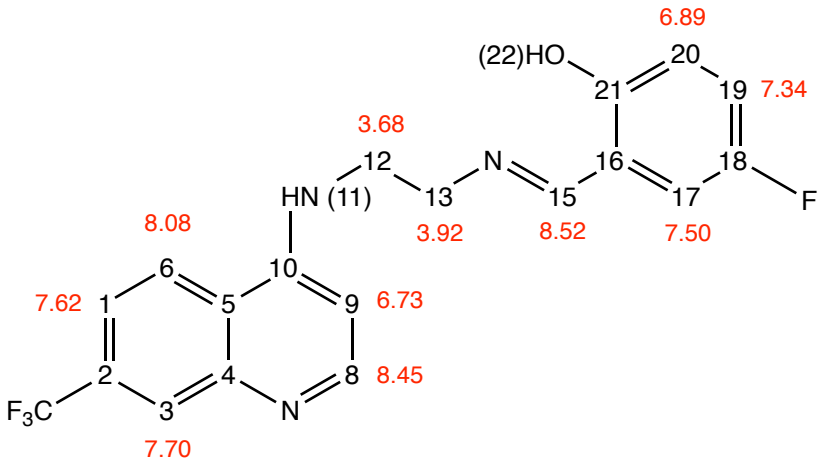
1. Ekengard, E. Half-sandwich complexes with aminoquinoline ligands – synthesis, antiplasmodial and antimycobacterial activities [dissertation on the Internet], Lund: Lund University; 2015 [cited 2021 Mar 14]. Available from:
2. Glans, L. Organometallic Complexes with Antimalarial Properties [dissertation on the Internet], Lund: Lund University; 2012 [cited 2021 Mar 21]. Available from:
3. WHO Malaria April 1, 2021 https://www.who.int/news-room/fact-sheets/detail/malaria
4. Kathryn N. Suh, Kevin C. Kain, and Jay S. Keystone, *Malaria*, 2004 May 25, NCBI
5. https://www.paho.org/en/topics/malaria
6. https://www.microscopemaster.com/plasmodium.html
7. Britannica, T. Editors of Encyclopaedia (2020, October 2). *Malaria*. *Encyclopedia Britannica*. https://www.britannica.com/science/malaria
8. https://en.wikipedia.org/wiki/Hemozoin#Formation
9. Lorena M. Coronado,Christopher T. Nadovich, and Carmenza Spadafora, *Malarial Hemozoin: From target to tool*, 2014 Feb 17, NCBI
10. Lotta Glans, Andreas Ehnbom, Carmen de Kock, Alberto Martínez, Jesús Estrada, Ebbe Nordlander, et al. *Ruthenium(II) arene complexes with chelating chloroquine analogue ligands: Synthesis, characterization and in vitro antimalarial activity*, Lund: Lund University; 2012
11. Lotta Glans, Andreas Ehnbom, Carmen de Kock, Alberto Martínez, Jesús Estrada, Ebbe Nordlander, et al. *Supporting Information Ruthenium(II) arene complexes with chelating chloroquine analogue ligands: Synthesis, characterization and in vitro antimalarial activity*, Lund: Lund University; 2012
12. Lotta Glans, Wanning Hu, Carmen de Kock, Peter J. Smith, Matti Haukka, Ebbe Nordlander et al. *Synthesis and antimalarial activity of cymantrene and cyrhetrene 4-aminoquinoline conjugates* Lund: Lund University; 2012
13. Erik Ekengard, Lotta Glans, Irwin Cassells, Thibault Fogeron, Preshendren Govender, Ebbe Nordlander et al. *Antimalarial activity of ruthenium(II) and osmium(II) arene complexes with mono- and bidentate chloroquine analogue ligands*, Lund: Lund University; 2015
14. Erik Ekengard, Kamlesh Kumar, Thibault Fogeron, Carmen de Kock, Peter J. Smith, Ebbe Nordlander et al. *Pentamethylcyclopentadienyl-Rhodium and Iridium complexes*

containing (N^N and N^O) bound chloroquine analogue ligands: synthesis, characterization and antimalarial properties, Lund: Lund University; 2015

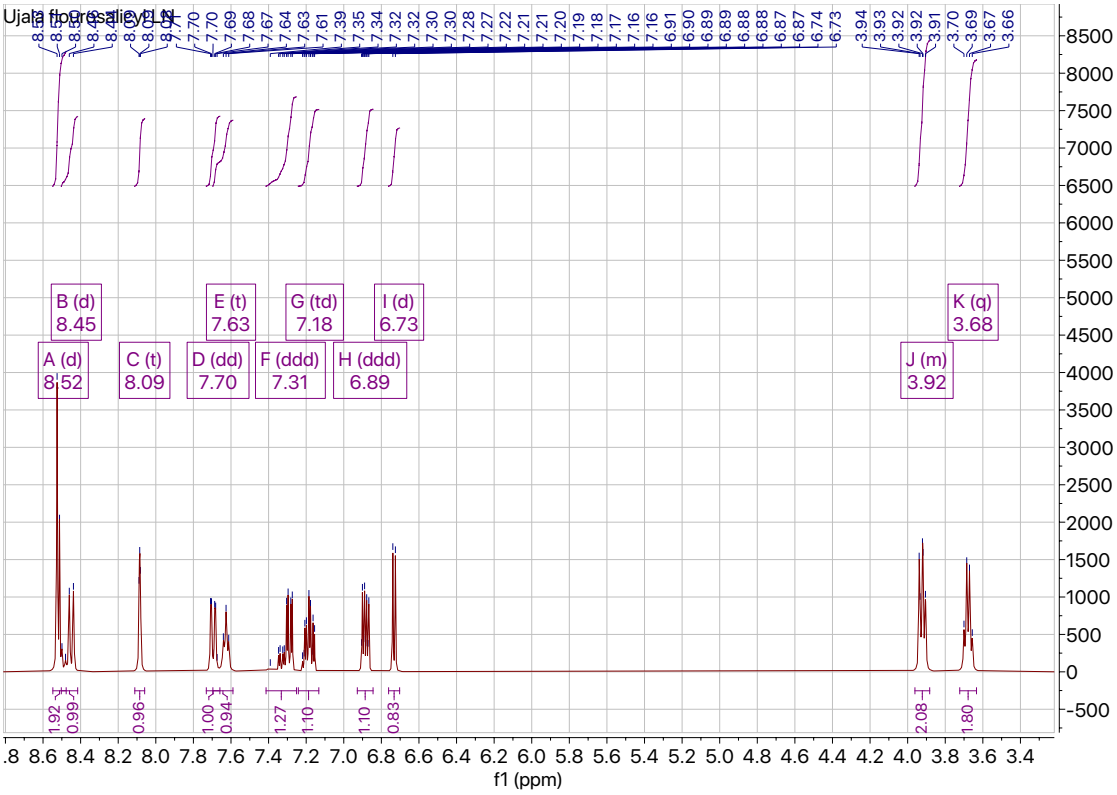
15. Liebman, K. New 4-Aminoquinoline Compounds to Reverse Drug Resistance in P. falciparum Malaria, and a Survey of Early European Antimalarial Treatments [dissertation on the Internet], Portland: Portland State University; 12-11-2014 [cited 2021]. Available from: https://pdxscholar.library.pdx.edu/open_access_etds/2114/
16. V. Raja Solomon, Sunil K. Puri, Kumkum Srivastava and S. B. Katti *Design and synthesis of new antimalarial agents from 4-aminoquinoline*, Lucknow: Division of Medicinal and Process Chemistry, Central Drug Research Institute; 8-12-2004
17. Kim Yearick, Kekeli Ekoue-Kovi, D. Iwaniuk, Jayakumar K. Natarajan, John Alumasa, Angel C. de Dios, et al. *Overcoming drug resistance to heme-targeted antimalarials by systematic side chain variation of 7-chloro-4-aminoquinolines*, Georgetown: Georgetown University 2008.

Appendix

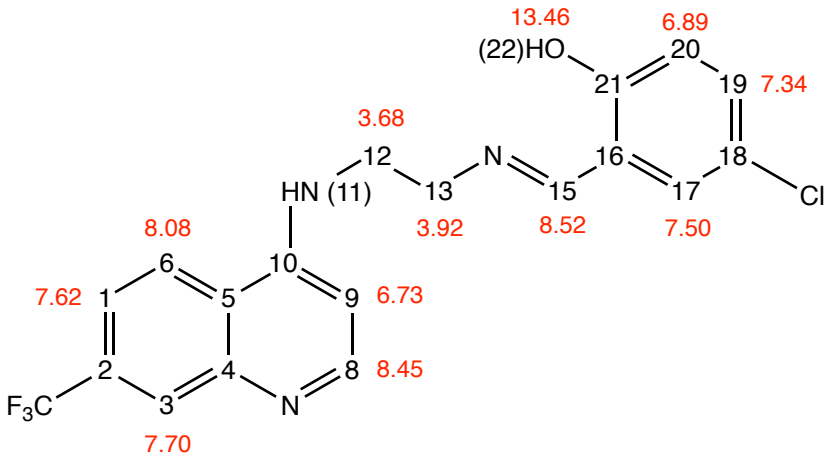
(E)-4-fluoro-2-(((2-((7-(trifluoromethyl)quinolin-4-yl)amino)ethyl)imino)methyl)phenol:



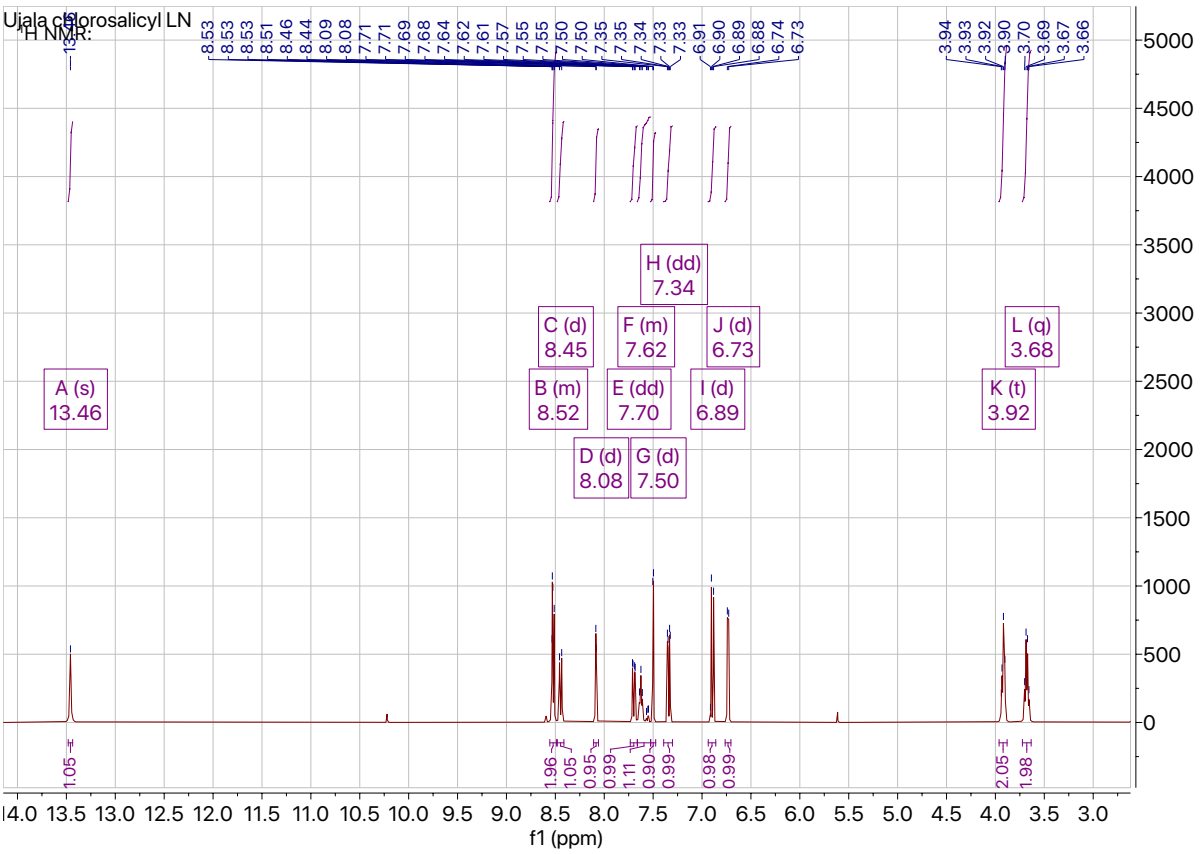
^{1}H NMR:



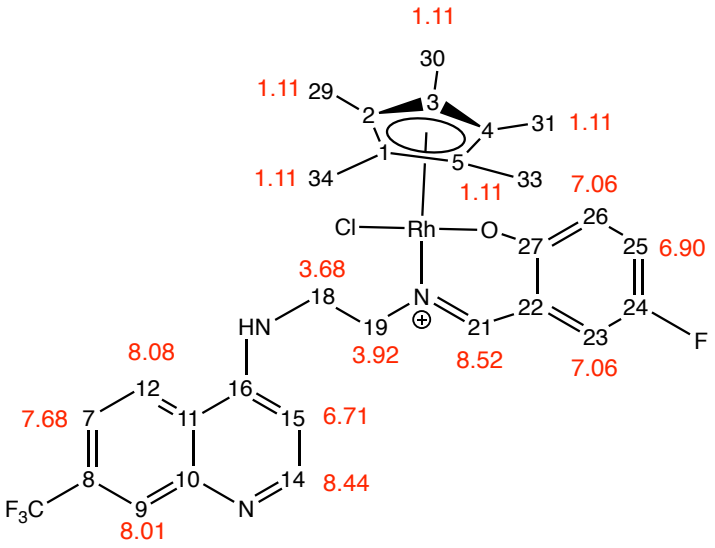
(*E*)-4-chloro-2-(((2-((7-(trifluoromethyl)quinolin-4-yl)amino)ethyl)imino) methyl)phenol ($L_{SAL(Cl)}$):



^{1}H NMR:



(η5-pentamethylcyclopentadienyl){(N-(2-((5-fluoro-2-hydroxyphenyl)methylimino) ethyl)-6-fluoroquinolin-4-amine)}chlororhodium(III), [RhCp*(LSAL(F))Cl]:



^{1}H NMR: